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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,748	TENNEKOON ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19 and 22-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19 and 22-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 8-28-06 has been entered. Claims 18, 19 and 22 have been amended. Claims 20 and 21 have been canceled. Claims 25-36 have been added. Claims 15-19 and 22-36 are pending and under consideration.

It should be noted that examiner for the instant application has been changed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 8-28-06 necessitates this new ground of rejection.

The term "hTERT" in line 5 of claim 19 is vague and renders the claim indefinite. The term "hTERT" is an abbreviation that can stands for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term "hTERT" would be remedial.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-18 and 22-24 remain rejected and the newly added claims 25-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and is repeated for the reasons set forth in the preceding Official action mailed 4-20-06. Applicant's arguments filed 8-28-06 have been fully considered but they are not persuasive.

Applicants argue that the specification teaches methods of treating patients with CNS disorders ([0065] and [0072]) and Bjorklund et al., 1985, teaches a method for grating cells into the CNS. Applicants cite US Patent 5,082,670 and argue that the '670 patent also cites Bjorklund et al., and the claimed method of the instant invention is enabled for defective, diseased, or damaged cells including those associated with Alzheimer's or Parkinson's or injury from physical trauma (amendment, p. 8-9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-20-06 and the following reasons.

Firstly, US Patent '670 is directed to the use of genetically modified donor cells from the same mammalian species and said donor cells express a functional molecule in a sufficient amount to ameliorate defective, diseased or damaged cells in CNS. However, the claimed method of the instant invention is directed to the use of neurons or oligodendrocyte differentiated from messenchymal stromal cells or oligodendrocyte precursor cells differentiated from messenchymal stromal cells to treat numerous neurological deterioration, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, trauma, or any metabolic lipid-storage disease, such as Tay-Sachs, GM1 gangliosidosis, adrenoleukodystrophy, Krabbe's

disease, metachromatic leukodystrophy, and multiple sclerosis, or damaged myelin in a subject. The subject matters of '670 and the instant invention differ dramatically from each other and they have to be considered individually. The conclusion of '670 cannot be extrapolated into the enablement of the claimed method of the instant invention.

Secondly, the claims of the instant invention encompass differentiation of messenchymal stromal cells (MSC) into neurons or oligodendrocyte in vitro or in vivo and allowing said differentiated cells to compensate for numerous different neurological deterioration including Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, trauma, or any metabolic lipid-storage disease including Tay-Sachs, GM1 gangliosidosis, adrenoleukodystrophy, Krabbe's disease, metachromatic leukodystrophy, and multiple sclerosis, or damaged myelin in a subject. The claims also encompass differentiation of messenchymal stromal cells in vitro into oligodendrocyte precursor cells and the use of said differentiated cells to compensate various neurological deterioration or damaged myelin in a subject. Different neurological disorders and metabolic lipid-storage diseases differ morphologically, physiologically and pathologically, and involve different types of neuronal cells or non-neuronal cells at different locations of a subject. Although the method of grafting cells was known in the art, however, the art of cell therapy in treating different disease or disorder in a subject was unpredictable at the time of the invention. The dosages of cells, the type of disease or disorder treated, the location of the target cells, and the administration routes are all important factors in determining the efficiency of the treatment of a particular neurological disease or disorder or a metabolic lipid-storage disease. The specification only shows the human MSC cells can differentiate into oligodendrocytes or neurons upon being injected into the lateral ventricles of myelin-deficient rats (Examples 4 and 5). The

specification fails to provide adequate guidance and evidence for how to administer MSC cells, neurons or oligodendrocytes differentiated from MSC cells, or oligodendrocyte precursor cells into a subject via various administration routes such that sufficient neurons or oligodendrocytes can be obtained at the target site so as to provide therapeutic effect in said subject for treating various neurological disease or disorder and metabolic lipid-storage diseases. There is no evidence of record that shows administration of MSC cells, neurons or oligodendrocytes differentiated from MSC cells, or oligodendrocyte precursor cells into a subject via various administration routes would be able to ameliorate symptoms of various disease or disorders as claimed. Thus, one skilled in the art at the time of the invention would not know how to administer MSC cells, neurons or oligodendrocytes differentiated from MSC cells, or oligodendrocyte precursor cells into a subject via various administration routes so as to provide therapeutic effect in said subject for treating various neurological disease or disorder and metabolic lipid-storage diseases. Therefore, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Thirdly, the specification only shows differentiation of MSC cells into oligodendrocyte precursor cells in vitro in a medium comprising B104 CM. There is no evidence of record in the specification or art that shows differentiation of MSC cells into oligodendrocyte precursor cells in vitro in a medium other than B104 CM. There is also no evidence of record that shows differentiation of MSC cells into neuronal cells in vitro in any medium. Thus, the claims are not enabled in differentiating MSC cells in vitro into oligodendrocyte precursor cells using medium other than B104 CM and use of said oligodendrocyte precursor cells for treating various diseases and disorders as claimed. The claims are not enabled in differentiating MSC cells in vitro into

neurons and use said neurons to treat various diseases and disorders as claimed. Claims 22-24, 26 and 32-34 read on using oligodendrocyte precursor cells capable of differentiating into oligodendrocytes for treating various neurological diseases and disorders. It was known that oligodendrocytes are non-neural cells. The specification fails to provide adequate guidance and evidence for how to use oligodendrocyte precursor cells or oligodendrocytes, which are non-neural cells, to compensate neurological deterioration and to treat numerous different neurological diseases and disorders as claimed. Thus, absent specific guidance, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants cite US Patent 7,022,231 are argue that a method of treating Parkinson's disease by administering cells transfected with a gene encoding a specific neurotropic factor is enabled, therefore, the claimed method of the instant invention is enabled (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-20-06 and the reasons set forth above. A method of treating Parkinson's disease by administering cells transfected with a gene encoding a specific neurotropic factor and the claimed method of the instant invention differ dramatically and has to be considered separately. Enablement of a method of treating Parkinson's disease with transfected with a gene encoding a specific neurotrophic factor does not mean that the claimed method of the instant invention is enabled. By the way, the cited US Patent 7,022,231 has claims directed to an apparatus incorporating potted hollow fibre membranes. Examiner is confused how this patent is relevant to a method of treating Parkinson's disease.

Applicants argue that the specification teaches that human MSC cells can be administered to mice via the lateral ventricle and the cells differentiate into oligodendrocytes and neurons. Applicants argue that the cited reference Orkin concerns with cystic fibrosis, which is irrelevant to the instant invention, and it is examiner's burden to give reasons for the lack of enablement (amendment, p. 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-20-06 and the reasons set forth above. Orkin shows that the data from animal models cannot be extrapolated into success in human in general. Therefore, the cited reference Orkin is relevant to the instant invention.

Applicants argue that the prior art teaches method of administration or grafting of cells into CNS and no undue experimentation is required to practice the claimed invention. Applicants cite Mezey that argues defects in the cited reference Castro, and argue murine bone marrow cells can give rise to neural cells and microglia in the brains of transplanted animals (amendment, p. 11-12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-20-06 and the reasons set forth above.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roecklein et al., 1995 (Blood, Vol. 85, No. 4, p. 997-1005) in view of MacKenzie et al., 2000 (Experimental Cell Research, Vol. 259, p. 336-350). Applicants' amendment filed 8-28-06 necessitates this new ground of rejection.

Claim 19 is directed to a composition consists of essentially of immortalized messenchymal stromal cells and a physiologically compatible carrier, wherein said cells comprise one or more exogenous genes and at least one of said exogenous genes is hTERT.

Roecklein teaches immortalizing human marrow stromal cells with a replication-defective recombinant retrovirus containing the human papilloma virus E6/E7 genes. Clone HS-5 supports proliferation of hematopoietic progenitor cells when cultured in serum-free medium with no exogenous factors (e.g. abstract). The medium is considered a physiologically compatible carrier.

Roecklein does not teach transforming the human marrow stromal cells with hTERT.

MacKenzie teaches that ectopic expression of the catalytic subunit of telomerase (hTERT) enables normal human cells to bypass senescence (M1) and oncogene transformed cells to avert crisis (M2) and become immortal. MacKenzie further teaches transducing primary human fetal lung fibroblasts (MRC-5 cells) with retroviral vector expressing hTERT and the

hTERT-transduced cells exhibit high level of telomerase activity and proliferation beyond senescence (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to transform human marrow stromal cells with a retroviral vector expressing hTERT because Roecklein teaches immortalizing human marrow stromal cells with a replication-defective recombinant retrovirus containing the human papilloma virus E6/E7 genes and MacKenzie teaches that a retroviral vector expressing hTERT can be used to immortalize or prolong proliferation beyond senescence of human cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to immortalize the human marrow stromal cells as taught by Roecklein or to prolong proliferation of the human cells beyond senescence as taught by MacKenzie with reasonable expectation of success.

Conclusion

No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER